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(19)(CA) **APPLICATION FOR CANADIAN PATENT** (12)

(54) Benzofurans

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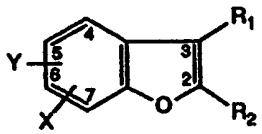
Benzofurans

Abstract

Compounds of formula I



(I),

wherein X, Y, R_1 and R_2 have the meanings given in the description, have valuable pharmaceutical properties and are effective especially against tumours. They are prepared in a manner known per se.

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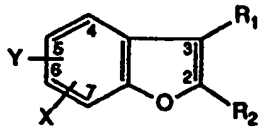
Benzofurans

The invention relates to compounds of formula I.



(I)

wherein X is halogen, cyano, carbamoyl, N-lower alkylcarbamoyl, N,N-di-lower alkylcarbamoyl, N,N-lower alkylenecarbamoyl; N,N-lower alkylenecarbamoyl interrupted by -O-, -S- or -NR"- wherein R" is hydrogen, lower alkyl or lower alkanoyl; N-cycloalkylcarbamoyl, N-(lower alkyl-substituted cycloalkyl)-carbamoyl, N-cycloalkyl-lower alkylcarbamoyl, N-(lower alkyl-substituted cycloalkyl)-lower alkylcarbamoyl, N-aryl-lower alkylcarbamoyl, N-arylcarbamoyl, N-hydroxycarbamoyl, hydroxy, lower alkoxy, aryl-lower alkoxy or aryloxy, Y is a $-CH_2$-A group in which A is imidazolyl, triazolyl or tetrazolyl bonded by way of a ring nitrogen atom, or Y is hydrogen, each of R_1 and R_2 independently of the other is hydrogen, lower alkyl or a $-CH_2$-A group as defined for Y, or R_1 and R_2 together are lower alkylene, with the proviso that one of the radicals Y, R_1 and R_2 is a $-CH_2$-A group, with the further proviso that, in a $-CH_2$-A group as the meaning of R_1 or R_2, A is other than 1-imidazolyl when X is bromine, cyano or carbamoyl, and with the proviso that, in a $-CH_2$-A group as the meaning of Y, A is other than 1-imidazolyl when X is halogen or lower alkoxy, R_1 is hydrogen and R_2 is hydrogen or lower alkyl, and salts thereof, to a process for the preparation of those compounds, to pharmaceutical compositions containing those compounds, to the use of those compounds for the therapeutic treatment of the human or animal body or for the preparation of pharmaceutical compositions.

Within the scope of this Application, the general definitions used hereinbefore and hereinafter have preferably the following meanings:

The prefix "lower" denotes a radical having up to and including 7, and especially up to and including 4, carbon atoms.

Lower alkyl is, for example, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, neopentyl, n-hexyl or n-heptyl, preferably ethyl and especially methyl.

Halogen is especially chlorine and more especially bromine, but may also be fluorine or iodine.

Halo-lower alkyl is, for example, trifluoromethyl.

Aryl is, for example, phenyl or naphthyl, such as 1- or 2-naphthyl. The phenyl and naphthyl radicals may be unsubstituted or substituted, especially as indicated below for phenyl. Aryl is preferably phenyl that is unsubstituted or substituted by from 1 to 4, especially 1 or 2, substituents from the group comprising lower alkyl, lower alkenyl, lower alkynyl, lower alkylene (attached to two adjacent carbon atoms), C_3-C_8cycloalkyl, phenyl-lower alkyl, phenyl, halo-lower alkyl, hydroxy, lower alkoxy, halo-lower alkoxy, phenyl-lower alkoxy, phenyloxy, lower alkenyloxy, halo-lower alkenyloxy, lower alkynyloxy, lower alkylenedioxy (attached to two adjacent carbon atoms), lower alkanoyloxy, phenyl-lower alkanoyloxy, phenylcarbonyloxy, mercapto, lower alkylthio, phenyl-lower alkylthio, phenylthio, lower alkylsulfinyl, phenyl-lower alkylsulfinyl, phenylsulfinyl, lower alkylsulfonyl, phenyl-lower alkylsulfonyl, phenylsulfonyl, halogen, nitro, amino, lower alkylamino, C_3- C_8cycloalkylamino, phenyl-lower alkylamino, phenylamino, di-lower alkylamino, N-lower alkyl-N-phenylamino, N-lower alkyl-N-phenyl-lower alkylamino; lower alkyleneamino or lower alkyleneamino interrupted by -O-, -S- or -NR"- (wherein R" is hydrogen, lower alkyl or lower alkanoyl); lower alkanoylamino, phenyl-lower alkanoylamino, phenylcarbonylamino, lower alkanoyl, phenyl-lower alkanoyl, phenylcarbonyl, carboxy, lower alkoxycarbonyl, carbamoyl, N-lower alkylcarbamoyl, N,N-di-lower alkylcarbamoyl, N,N-lower alkylenecarbamoyl; N,N-lower alkylenecarbamoyl interrupted by -O-, -S- or -NR"- wherein R" is hydrogen, lower alkyl or lower alkanoyl; N-hydroxycarbamoyl, N-phenyl-lower alkylcarbamoyl, N-phenylcarbamoyl, cyano, sulfo, lower alkoxysulfonyl, sulfamoyl, N-lower alkyl-sulfamoyl, N,N-di-lower alkylsulfamoyl and N-phenylsulfamoyl; wherein the phenyl groups occurring within the substituents are in each case unsubstituted or substituted in their turn by lower alkyl, lower alkoxy, hydroxy, halogen and/or by trifluoromethyl.

Aryl is especially phenyl that is unsubstituted or substituted by lower alkyl, lower alkoxy, hydroxy, halogen and/or by trifluoromethyl, and is most especially phenyl.

Substituted phenyl is preferably di-substituted and especially mono-substituted.

Aryl-lower alkoxy is, for example, phenyl-lower alkoxy and especially benzyloxy.

N-arylcarbamoyl is, for example, N-phenylcarbamoyl.

Imidazolyl bonded by way of a ring nitrogen atom is, for example, 1-imidazolyl.

Triazolyl bonded by way of a ring nitrogen atom is, for example, 1-(1,2,4-triazolyl), 1-(1,3,4-triazolyl), 1-(1,2,3-triazolyl) or 1-(1,2,5-triazolyl).

Tetrazolyl bonded by way of a ring nitrogen atom is, for example, 1-tetrazolyl or 2-tetrazolyl.

Lower alkylene formed by the groups R_1 and R_2 is preferably a $-(CH_2)_n-$ radical wherein n is 3, 4 or 5, especially 3 or 4, for example 1,3-propylene or especially 1,4-butylene, but may also be substituted, for example by lower alkyl.

Cycloalkyl is preferably C_3-C_8- and especially C_3- or C_5-C_6cycloalkyl, which is intended to mean that it contains from 3 to 8 and 3, 5 or 6 ring carbon atoms, respectively.

Lower alkylene attached to two adjacent carbon atoms of a benzene ring is preferably C_3-C_4alkylene, for example 1,3-propylene or 1,4-butylene.

Lower alkylenedioxy attached to two adjacent carbon atoms is preferably C_1-C_2alkylenedioxy, for example methylenedioxy or 1,2-ethylenedioxy.

Lower alkyleneamino is, for example, C_4-C_7alkyleneamino and especially C_4-C_5-alkyleneamino, for example piperidino. Lower alkyleneamino interrupted by -O-, -S- or -NR"- is, for example, such a C_4-C_7- and especially C_4-C_5alkyleneamino group in which one ring carbon atom has been replaced by the corresponding hetero group, and is especially morpholino, thiomorpholino, piperazino or 4-lower alkyl- or 4-acyl-piperazino. Carbamoyl denotes the $-CONH_2$ group. Accordingly, N,N-lower alkylenecarbamoyl, for example, is lower alkyleneamino-carbonyl in which lower alkyleneamino is as defined above.

Salts of compounds according to the invention are especially pharmaceutically acceptable non-toxic salts. For example, compounds of formula I having basic groups can form acid addition salts, for example with inorganic acids, such as hydrochloric acid, sulfuric acid or phosphoric acid, or with suitable organic carboxylic or sulfonic acids, for example acetic acid, fumaric acid or methanesulfonic acid, or with amino acids, such as arginine or lysine. Compounds of formula I having an acid group, for example 1-tetrazolyl, form, for example, metal salts or ammonium salts, such as alkali metal and alkaline earth metal salts, for example sodium, potassium, magnesium or calcium salts, and ammonium salts with ammonia or suitable organic amines, such as lower alkylamines, for example triethylamine, hydroxy-lower alkylamines, for example 2-hydroxyethylamine, bis(2-hydroxyethyl)amine or tris(2-hydroxyethyl)amine, basic aliphatic esters of carboxylic acids, for example 4-aminobenzoic acid 2-diethylaminoethyl ester, lower alkyleneamines, for example 1-ethylpiperidine, cycloalkylamines, for example dicyclohexylamine, or benzylamines, for example N,N'-dibenzylethylenediamine, dibenzylamine or benzyl-b-phenethylamine. Compounds of formula I having an acid group and a basic group may also be in the form of internal salts, that is to say in zwitterionic form.

For the purpose of isolation or purification it is also possible to use pharmaceutically unsuitable salts, for example picrates or perchlorates. Only the pharmaceutically acceptable non-toxic salts are used therapeutically and these are therefore preferred.

The compounds of formula I according to the invention have valuable, especially pharmacologically useful, properties. In particular, they selectively inhibit the enzyme aromatase in mammals, including humans. As a result, the metabolic conversion of androgens to oestrogens is inhibited. The compounds of formula I are therefore suitable, for example, for the treatment of oestrogen-dependent diseases, including oestrogen-dependent breast cancer, especially in post-menopausal women. They are also useful, for example, in the treatment of gynaecomastia, i.e. breast development in males, since the aromatisation of the steroids is inhibited.

These effects can be demonstrated by in vitro tests or in vivo tests, preferably on mammals, for example guinea pigs, mice, rats, cats, dogs or apes. The dosage used is, for example, within a range of approximately from 0.001 to 10 mg/kg, preferably from 0.001 to 1 mg/kg.

The in vitro inhibition of aromatase activity can be demonstrated, for example, using the method described in J. Biol. Chem. 249, 5364 (1974). IC_{50} values for aromatase inhibition can furthermore be obtained, for example, in vitro from enzyme-kinetic studies concerned with the inhibition of the conversion of 4-^{14}C-androstenedione to 4-^{14}C-oestrone in human placental microsomes. The IC_{50} values of the compounds according to the invention are, at the minimum, about 10^{-9} M.

In vivo, aromatase inhibition can be demonstrated, for example, by the suppression of the ovarian oestrogen content of female rats that are injected first with mare's serum gonadotrophin and, 2 days later, with human chorionic gonadotrophin, and treated p.o. the next day with a compound of the invention and, 1 hour later, with androstenedione. A further possible method of determining aromatase inhibition in vivo is described hereafter: androstenedione (30 mg/kg subcutaneously) is administered on its own or together with a compound of the invention (orally or subcutaneously) for 4 days to sexually immature female rats. After the fourth administration, the rats are sacrificed and the uteri are isolated and weighed. The aromatase inhibition is determined by the extent to which the hypertrophy of the uterus caused by the administration of androstenedione on its own is suppressed or reduced by the simultaneous administration of the compound according to the invention. The minimum effective dose of the compounds of the invention in the in vivo tests is approximately from 0.001 to 1 mg/kg.

The anti-tumoral activity, especially in the case of oestrogen-dependent tumours, can be demonstrated in vivo, for example in DMBA-induced mammary tumours in female Sprague-Dawley rats [cf. Proc. Soc. Exp. Biol. Med. 160, 296-301 (1979)]. The use of compounds according to the invention brings about a regression of the tumours and furthermore suppresses the occurrence of new tumours at daily doses of about 1 mg/kg and above p.o.

In addition, the compounds of formula I do not have an inhibiting effect on the cleavage of the cholesterol side-chain and do not induce adrenal hypertrophy, as is demonstrated by investigation of the endocrine system.

On account of their pharmacological properties as extremely selective inhibitors of the enzyme aromatase, the compounds of formula I are suitable, for example, for the treatment of oestrogen-dependent diseases, such as breast tumours (breast carcinoma), endometriosis, premature labour or endometrial tumours in women, or of gynaecomastia

in men.

The invention relates especially to the compounds of formula I wherein X is halogen, cyano, carbamoyl, N-lower alkylcarbamoyl, N-cycloalkyl-lower alkylcarbamoyl, N,N-di-lower alkylcarbamoyl, N-arylcarbamoyl, hydroxy, lower alkoxy, aryl-lower alkoxy or aryloxy, wherein aryl is phenyl or naphthyl each of which is unsubstituted or substituted by lower alkyl, hydroxy, lower alkoxy, halogen and/or by trifluoromethyl; Y is a $-CH_2-A$ group in which A is 1-imidazolyl, 1-(1,2,4-triazolyl), 1-(1,3,4-triazolyl), 1-(1,2,3-triazolyl), 1-(1,2,5-triazolyl), 1-tetrazolyl or 2-tetrazolyl, or Y is hydrogen; each of R_1 and R_2 independently of the other is hydrogen, lower alkyl or a $-CH_2-A$ group as defined for Y, or R_1 and R_2 together are $-(CH_2)_n-$ wherein n is 3, 4 or 5; with the proviso that one of the radicals Y, R_1 and R_2 is a $-CH_2-A$ group, with the further proviso that, in a $-CH_2-A$ group as the meaning of R_1 or R_2, A is other than 1-imidazolyl when X is bromine, cyano or carbamoyl, and with the proviso that, in a $-CH_2-A$ group as the meaning of Y, A is other than 1-imidazolyl when X is halogen or lower alkoxy, R_1 is hydrogen and R_2 is hydrogen or lower alkyl, and salts thereof.

The invention relates preferably to the compounds of formula I wherein the radical X is attached in the 5- or 7-position and is halogen, cyano, carbamoyl or phenyloxy; the radical Y is attached in the 4- or 5-position and is a $-CH_2-A$ group in which A is 1-imidazolyl, 1-(1,2,4-triazolyl), 1-(1,2,3- triazolyl), 1-tetrazolyl or 2-tetrazolyl, or the radical Y is hydrogen; R_1 is hydrogen, lower alkyl or a $-CH_2-A$ group as defined for Y, R_2 is hydrogen or lower alkyl, or R_1 and R_2 together are $-(CH_2)_4-$; with the proviso that one of the radicals Y and R_1 is a $-CH_2-A$ group; with the further proviso that, in a $-CH_2-A$ group as the meaning of R_1, A is other than 1-imidazolyl when X is bromine, cyano or carbamoyl, and with the proviso that, in a $-CH_2-A$ group as the meaning of Y, A is other than 1-imidazolyl when X is halogen and R_1 is hydrogen; and salts thereof.

Prominence is to be given to the compounds of formula I wherein the radical X is attached in the 5- or 7-position and is halogen, cyano, carbamoyl or phenyloxy; the radical Y is attached in the 4- or 5-position and is a $-CH_2-A$ group in which A is 1-(1,2,4-triazolyl), 1-(1,2,3-triazolyl), 1-tetrazolyl or 2-tetrazolyl, or the radical Y is hydrogen; R_1 is hydrogen, lower alkyl or a $-CH_2-A$ group as defined for Y, R_2 is hydrogen or lower alkyl, or R_1 and R_2 together are $-(CH_2)_4-$; with the proviso that one of the radicals Y and R_1 is a $-CH_2-A$ group; and salts thereof.

The invention relates especially preferably to compounds of formula I wherein the radical X is attached in the 5- or 7-position and is halogen, cyano, carbamoyl or phenyloxy; the radical Y is attached in the 4- or 5-position and is a $-CH_2-A$ group in which A is 1-imidazolyl, 1-(1,2,4-triazolyl), 1-(1,2,3-triazolyl), 1-tetrazolyl or 2-tetrazolyl; each of R_1 and R_2 independently of the other is hydrogen or lower alkyl, or R_1 and R_2 together are $-(CH_2)_4-$; with the proviso that, in a group Y = $-CH_2-A$, A is other than 1-imidazolyl when X is halogen and R_1 is hydrogen; and salts thereof.

Preference is also given to the compounds of formula I wherein the radical X is attached in the 5- or 7-position and is halogen, cyano, carbamoyl or phenyloxy; the radical Y is hydrogen; R_1 is a $-CH_2-A$ group in which A is 1-imidazolyl, 1-(1,2,4-triazolyl), 1-(1,2,3-triazolyl), 1-tetrazolyl or 2- tetrazolyl, R_2 is hydrogen or lower alkyl; with the proviso that, in a group R_1 = $-CH_2-A$, A is other than 1-imidazolyl when X is bromine, cyano or carbamoyl; and salts thereof.

Special preference is given to the compounds of formula I wherein the radical X is attached in the 7-position and is bromine, cyano, carbamoyl or phenyloxy; the radical Y is attached in the 4-position and is a $-CH_2-A$ group in which A is 1-imidazolyl, 1-(1,2,4-triazolyl), 1-tetrazolyl or 2-tetrazolyl; each of R_1 and R_2 independently of the other is lower alkyl, or R_1 and R_2 together are $-(CH_2)_4-$; and salts thereof.

Prominence is also to be given to the compounds of formula I wherein X is halogen, cyano, carbamoyl, hydroxy, lower alkoxy or phenyloxy, wherein phenyl is unsubstituted or substituted by lower alkyl, hydroxy, lower alkoxy, halogen and/or by trifluoromethyl, Y is a $-CH_2-A$ group in which A is 1-imidazolyl, 1-(1,2,4-triazolyl), 1-(1,3,4-triazolyl), 1-(1,2,3-triazolyl), 1-(1,2,5-triazolyl), 1-tetrazolyl or 2-tetrazolyl, R_1 is lower alkyl, R_2 is hydrogen or lower alkyl, or R_1 and R_2 together are $-(CH_2)_n-$ wherein n is 3 or 4, and salts thereof.

Special prominence is to be given to the compounds of formula I wherein the radical X is attached in the 4- or 7-position and is halogen, cyano, carbamoyl or phenyloxy; the radical Y is attached in the 4- or 5-position and is a $-CH_2-A$ group in which A is 1-imidazolyl, 1-(1,2,4-triazolyl), 1-(1,2,3- triazolyl), 1-tetrazolyl or 2-tetrazolyl, R_1 is lower alkyl, R_2 is hydrogen or lower alkyl, or R_1 and R_2 together are $-(CH_2)_4-$; and salts thereof.

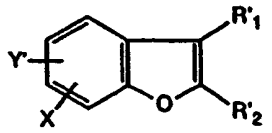
As sub-groups of a group of compounds of formula I, prominence is to be given to each of

the following: (a) compounds of formula I wherein the radical X is attached in the 7-position and the radical Y is attached in the 4-position; (b) compounds of formula I wherein X is bromine or cyano; (c) compounds of formula I wherein X is carbamoyl; (d) compounds of formula I wherein Y is a $-CH_2-A$ group in which A is 1-imidazolyl or 1-(1,2,4-triazolyl).

The invention relates most especially to the specific compounds described in the Examples and to pharmaceutically acceptable salts thereof.

The compounds of formula I can be prepared in a manner known per se, for example by

(a) condensing a reactive esterified derivative of a hydroxymethyl compound of formula II



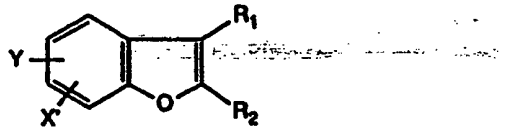
(II)

wherein one of the radicals Y', R'_1 and R'_2 is hydroxymethyl and the other two radicals have the definitions given for Y, R_1 and R_2, respectively, under formula I, and X is as defined under formula I, with a compound

A - H (III),

wherein A is as defined under formula I, or with an N-protected derivative thereof, or

(b) in a compound of formula IV

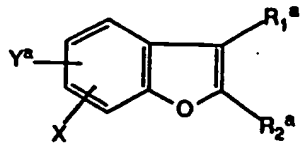


(IV)

wherein X' is a radical that can be converted into a group X, and Y, R_1 and R_2 are as defined under formula I, converting the radical X' into a group X, or

(c) for the preparation of compounds of formula I wherein A in the group $-CH_2-A$ is

1-tetrazolyl, reacting a compound of formula V



(V),

wherein one of the radicals Y^a, $R_1{}^a$ and $R_2{}^a$ is isocyanomethyl and the other two radicals have the definitions given for Y, R_1 and R_2, respectively, under formula I, and X is as defined under formula I, with hydrazoic acid or, especially, with a salt thereof; and/or, if desired, converting a resulting compound of formula I into another compound of formula I, and/or, if desired, converting a resulting salt into the free compound or into another salt, and/or, if desired, converting a resulting free compound of formula I having salt-forming properties into a salt, and/or separating a resulting mixture of isomeric compounds of formula I into the individual isomers.

In the following, more detailed description of processes a), b) and c), unless indicated to the contrary, each of the symbols X, Y, A, R_1 and R_2 has the meaning given under formula I.

Process (a): In a compound of formula II, reactive esterified hydroxymethyl is hydroxymethyl that has been esterified by a leaving group, for example lower alkylsulfonyloxymethyl or arylsulfonyloxymethyl, such as methylsulfonyloxymethyl or p- toluenesulfonyloxymethyl, or halomethyl, for example chloromethyl, bromomethyl or iodomethyl.

If, in the reaction according to process (a), 1,2,4-triazole is used as the compound of formula III, then - depending on the reaction conditions chosen - mixtures of compounds of formula I wherein A is 1-(1,2,4-triazolyl) and 1-(1,3,4-triazolyl) are normally obtained, which can be separated, for example, by chromatography. Correspondingly, if 1,2,3-triazole is used as the compound of formula III, then mixtures of compounds of formula I wherein A is 1-(1,2,3-triazolyl) and 1-(1,2,5-triazolyl) are normally obtained, which similarly can be separated, for example, by chromatography. Correspondingly, if tetrazole is used as the compound of formula III, then mixtures of compounds of formula I wherein A is 1-tetrazolyl and 2-tetrazolyl are normally obtained, which similarly can readily be separated, for example, by chromatography. In some cases it is possible, by using compounds of formula III in which a specific ring nitrogen atom has been protected by a

protecting group, to obtain selectively only one of the two compounds in question.

Suitable protecting groups for a ring nitrogen atom in a compound of formula III are, for example, tri-lower alkylsilyl, for example trimethylsilyl, lower alkanoyl, for example acetyl, N,N-di-lower alkylcarbamoyl, for example N,N-dimethylcarbamoyl, or triaryl-methyl, for example triphenylmethyl.

Another suitable protecting group is amino or ammonium, which is useful especially in the selective preparation of 1-(1,2,4-triazolyl) compounds. For that purpose, in the reaction according to process (a), 4H-1,2,4-triazole-4-amine (= 1-amino-1,3,4-triazole) is used as the compound of formula III. A quaternary 1-benzofuranylmethyl-4-amino-1,2,4-triazolium compound is initially obtained, which is converted into the desired 1-benzofuranylmethyl-1,2,4-triazolyl compound of formula I, for example by treatment with hydrochloric acid, 50 % hypophosphorous acid (H_3PO_2) and sodium nitrite.

The condensation reaction according to process (a) is known per se and corresponds to a conventional N-alkylation that is carried out, for example, without the addition of bases or, preferably, in the presence of bases, such as, for example, potassium carbonate, sodium, triethylamine or pyridine.

The starting compounds of formula II are preferably obtained in a manner known per se, by esterification, from the corresponding hydroxymethyl compounds. The hydroxymethyl compounds can be obtained, for example, by reduction, for example with $LiAlH_4$ or diisobutylaluminium hydride, from the corresponding carboxy or lower alkoxycarbonyl compounds. The latter are known per se or can be prepared analogously to known substituted benzofurancarboxylic acids and esters (cf. also Examples 1 and 6).

Process (b): Radicals X' that can be converted into a group X are, for example, amino that can be converted, for example via diazotisation, for example into halogen, cyano or hydroxy, or carboxy, lower alkoxycarbonyl, halocarbonyl, for example -COCl, or an acid anhydride, which can be converted by reaction with ammonia or the corresponding primary or secondary amine into carbamoyl or N-mono- or N,N-di-substituted carbamoyl, respectively. The conversion of substituents on aromatic systems according to process (b) is known per se.

The starting compounds of formula IV are prepared, for example, analogously to

process (a), there being used in the corresponding reactions, instead of the radical X, a radical X'.

Process (c): Isocyanomethyl is a $-CH_2-N=C$ radical. Salts of hydrazoic acid are especially alkali metal azides, for example sodium azide.

The starting compounds of formula V are prepared, for example, from the analogous compounds of formula II in which one of the radicals Y', R'_1 and R'_2 is, for example, bromomethyl. The latter compounds are first converted in a manner known per se, for example by reaction with hexamethylenetetramine (urotropine), into the corresponding aminomethyl compounds, and then converted in a manner known per se, for example by reaction with dichlorocarbene (for example from chloroform and concentrated KOH), into the desired isocyanomethyl compounds of formula V.

Compounds of formula I can be converted in a manner known per se into other compounds of formula I.

For example, compounds of formula I wherein X is halogen, especially bromine, can be converted by reaction with a cyanating agent, for example copper(I) cyanide, into other compounds of formula I wherein X is cyano.

It is also possible, for example, to convert compounds of formula I wherein X is halogen, especially bromine, by reaction with hydroxyaryl compounds or corresponding alkali metal salts thereof, for example potassium phenolate, into other compounds of formula I wherein X is aryloxy, advantageously, for example, in the presence of copper.

Furthermore, for example, compounds of formula I wherein X is cyano can be converted by partial hydrolysis, for example with potassium carbonate and aqueous H_2O_2 solution, into other compounds of formula I wherein X is carbamoyl.

On the other hand, for example, compounds of formula I wherein X is carbamoyl or N-lower alkylcarbamoyl can also be converted, with the splitting-off of water or lower alkanol, respectively, into compounds of formula I wherein X is cyano.

Finally, compounds of formula I wherein X is cyano can also be converted directly into compounds of formula I wherein X is, for example, N-lower alkylcarbamoyl or N-cyclo-

alkyl-lower alkylcarbamoyl by first being treated with KOH/tert-butanol and then reacted with a lower alkyl halide or a cycloalkyl-lower alkyl halide, respectively [S. Linke, Synthesis 1978, 303].

Free compounds of formula I having salt-forming properties that are obtainable according to the process can be converted into their salts in a manner known per se: compounds having basic properties, for example by treatment with acids or suitable derivatives thereof, and compounds having acid properties, for example by treatment with bases or suitable derivatives thereof.

Mixtures of isomers obtainable according to the invention can be separated into the individual isomers in a manner known per se, racemates, for example, by forming salts with optically pure salt-forming reagents and separating the diastereoisomeric mixture so obtainable, for example by means of fractional crystallisation.

The reactions described above can be carried out under reaction conditions that are known per se, in the absence or, usually, in the presence of solvents or diluents, preferably those which are inert towards the reagents used and are solvents thereof, in the absence or presence of catalysts, condensing agents or neutralising agents, and, depending on the nature of the reaction and/or of the reactants, at reduced, normal or elevated temperature, for example within a temperature range of from approximately -70°C to approximately 200°C, preferably from approximately -20°C to approximately 150°C, for example at the boiling point of the solvent used, under atmospheric pressure or in a closed vessel, where appropriate under pressure, and/or in an inert atmosphere, for example under a nitrogen atmosphere.

In view of the close relationship between the compounds of formula I in free form and in the form of salts, hereinbefore and hereinafter any reference to the free compounds or their salts should be understood as including also the corresponding salts or free compounds, respectively, where appropriate and expedient.

The compounds, including their salts, may also be obtained in the form of hydrates, or their crystals may, for example, include the solvent used for crystallisation.

The starting materials used in the process of the present invention are preferably those which result in the compounds described at the beginning as being especially valuable.

The invention relates also to those forms of the process in which a compound obtainable as intermediate at any stage of the process is used as starting material and the remaining process steps are carried out, or in which a starting material is formed under the reaction conditions or is used in the form of a derivative, for example a salt thereof.

The present invention relates also to pharmaceutical compositions that contain one of the pharmacologically active compounds of formula I as active ingredient. Compositions for enteral, especially oral, administration and for parenteral administration are especially preferred. The compositions contain the active ingredient on its own or, preferably, together with a pharmaceutically acceptable carrier. The dosage of the active ingredient depends upon the disease to be treated and upon the species, its age, weight and individual condition, and also upon the mode of administration.

The pharmaceutical compositions contain from approximately 0.1 % to approximately 95 % active ingredient, forms of administration that are in single-dose form preferably containing from approximately 1 % to approximately 90 % active ingredient, and forms of administration that are not in single-dose form preferably containing from approximately 0.1 % to approximately 20 % active ingredient. Unit dose forms, such as drages, tablets or capsules, contain from approximately 0.5 mg to approximately 100 mg of active ingredient.

The pharmaceutical compositions of the present invention are prepared in a manner known per se, for example by means of conventional mixing, granulating, confectioning, dissolving or lyophilising processes. For example, pharmaceutical compositions for oral administration can be obtained by combining the active ingredient with one or more solid carriers, if desired granulating a resulting mixture and, if desired, processing the mixture or granulate into tablets or dragee cores, where appropriate by adding additional excipients.

Suitable carriers are especially fillers, such as sugars, for example lactose, saccharose, mannitol or sorbitol, cellulose preparations and/or calcium phosphates, for example tricalcium phosphate or calcium hydrogen phosphate, and binders, such as starches, for example corn, wheat, rice or potato starch, methylcellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose and/or polyvinylpyrrolidone, and/or, if desired, disintegrators, such as the above-mentioned starches, also carboxymethyl starch,

crosslinked polyvinylpyrrolidone, alginic acid or a salt thereof, such as sodium alginate. Additional excipients are especially flow conditioners and lubricants, for example silica, talc, stearic acid or salts thereof, such as magnesium or calcium stearate, and/or polyethylene glycol, or derivatives thereof.

Dragee cores may be provided with suitable coatings which may be enteric coatings, there being used, inter alia, concentrated sugar solutions which may contain gum arabic, talc, polyvinylpyrrolidone, polyethylene glycol and/or titanium dioxide, or coating solutions in suitable organic solvents or solvent mixtures, or, for the preparation of enteric coatings, solutions of suitable cellulose preparations, such as acetylcellulose phthalate or hydroxypropylmethylcellulose phthalate. Dyes or pigments may be added to the tablets or drage coatings, for example for identification purposes or to indicate different doses of active ingredient.

Other orally administrable pharmaceutical compositions are dry-filled capsules consisting of gelatin, and also soft sealed capsules consisting of gelatin and a plasticiser, such as glycerol or sorbitol. The dry-filled capsules may contain the active ingredient in the form of a granulate, for example in admixture with fillers, such as corn starch, binders and/or glidants, such as talc or magnesium stearate, and, if desired, stabilisers. In soft capsules, the active ingredient is preferably dissolved or suspended in suitable liquid excipients, such as fatty oils, paraffin oil or liquid polyethylene glycols, to which stabilisers may also be added.

Other oral dosage forms are, for example, syrups prepared in customary manner that contain the active ingredient, for example, in suspended form and in a concentration of approximately from 5 % to 20 %, preferably approximately 10 % or in a similar concentration that provides a suitable single dose when the syrup is administered in quantities of 5 or 10 ml. Also suitable, for example, are powdered or liquid concentrates for the preparation of shakes, for example in milk. Such concentrates may also be packaged in single dose quantities.

Suitable rectally administrable pharmaceutical compositions are, for example, suppositories that consist of a combination of the active ingredient with a suppository base. Suitable suppository bases are, for example, natural or synthetic triglycerides, paraffin hydrocarbons, polyethylene glycols or higher alkanols.

For parenteral administration there are suitable, especially, aqueous solutions of an active ingredient in water-soluble form, for example in the form of a water-soluble salt, or aqueous injection suspensions that contain viscosity-increasing substances, for example sodium carboxymethylcellulose, sorbitol and/or dextran and, if desired, also stabilisers. In this case, the active ingredient, if desired together with excipients, may also be in the form of a lyophilisate and be dissolved by the addition of suitable solvents before parenteral administration.

Solutions, such as are used, for example, for parenteral administration, may also be administered in the form of infusion solutions.

The invention relates also to a method for the treatment of the pathological conditions mentioned above. The compounds of the present invention can be administered prophylactically or therapeutically, and are preferably used in the form of pharmaceutical compositions. For a body weight of approximately 70 kg, a daily dose of from approximately 0.5 mg to approximately 100 mg, preferably from approximately 1 mg to approximately 20 mg, of a compound of the present invention will be administered.

The following Examples illustrate the present invention; temperatures are given in degrees Celsius. The following abbreviations are used: ether = diethyl ether; THF = tetrahydrofuran; hexane = n-hexane; DMF = dimethylformamide; DMSO = dimethyl sulfoxide; TLC = thin-layer chromatography.

Example 1: 7-Bromo-4-[1-(1,2,4-triazolyl)methyl]-2,3-dimethylbenzofuran

104 mg of 1,2,4-triazole, 139 mg of potassium carbonate and 10 mg of potassium iodide are added in succession to a solution of 318 mg of 7-bromo-4-bromomethyl-2,3-dimethylbenzofuran in 10 ml of absolute acetone. After stirring for 2 hours at 55°, the suspension is cooled to room temperature and the acetone is evaporated. The reaction mixture is partitioned between methylene chloride and water, and the organic phase is washed with brine, dried over sodium sulfate and concentrated to dryness by evaporation. The resulting oil is chromatographed with chloroform over silica gel to yield the title compound. It is recrystallised from methylene chloride/ether/hexane; m.p. 108-110°. IR (CH_2Cl_2): 1631, 1605, 1504, 1404, 1199, 1140 cm^{-1}.

The starting compounds are prepared as follows:

(a) 4-Bromo-3-(butan-3-on-2-yl)oxy-benzoic acid ethyl ester

5.17 g of potassium carbonate in 20.5 ml of acetone are added to 3.08 g of 4-bromo-3-hydroxybenzoic acid ethyl ester (see DE-A-2 062 611) and 1.46 g of 3-chloro-2-butanone. After stirring under reflux for 16 hours, the sand-yellow suspension is cooled to room temperature and filtered. The filtrate is concentrated by evaporation under reduced pressure to yield the title compound in the form of a colourless oil that is used further without further purification. TLC (silica gel; CH_2Cl_2/methanol 95:5) $R_f = 0.69$. IR (CH_2Cl_2): 1720, 1590, 1575, 1480, 1415, 1290 cm^{-1}.

(b) 7-Bromo-2,3-dimethylbenzofuran-4-carboxylic acid

34 g of 4-bromo-3-(butan-3-on-2-yl)oxy-benzoic acid ethyl ester are added dropwise within 20 minutes to 25 ml of ice-cooled concentrated sulfuric acid. The mixture is stirred under nitrogen for 25 hours (bath temperature: 50°). The reaction mixture is first poured onto a mixture of ice-water and ethyl acetate and then partitioned between ethyl acetate and saturated aqueous sodium hydrogen carbonate solution. The aqueous phase is separated off and washed twice with ethyl acetate. The combined organic extracts are extracted again with aqueous sodium hydrogen carbonate solution. The combined aqueous extracts are adjusted to pH 1 with concentrated hydrochloric acid, a yellow solid precipitating which is removed by filtration. After recrystallisation from ether, the title compound is obtained. TLC (silica gel; toluene/ethyl acetate 9:1) $R_f = 0.3$. IR (DMSO-d_6): 1710, 1625, 1260, 1170 cm^{-1}.

(c) 7-Bromo-4-hydroxymethyl-2,3-dimethylbenzofuran

1.58 g of 7-bromo-2,3-dimethylbenzofuran-4-carboxylic acid are added in portions to a suspension, cooled to 0°, of 226.3 mg of lithium aluminium hydride in 18 ml of absolute THF. When the addition is complete, the solution is stirred further for 30 minutes at 0° and then for 19 hours at room temperature. The reaction mixture is then partitioned between 1N hydrochloric acid and ethyl acetate. The aqueous phase is separated off and the organic phase is washed twice with aqueous sodium hydrogen carbonate solution and twice with brine. The organic phase is dried over sodium sulfate and the solvent is evaporated off under reduced pressure to yield the title compound in the form of a light-yellow solid. TLC (CH_2Cl_2/methanol 95:5) $R_f = 0.5$. IR (CH_2Cl_2): 3597, 2923, 1632, 1602, 1404, 1206 cm^{-1}.

(d) 7-Bromo-4-bromomethyl-2,3-dimethylbenzofuran

1.98 g of 7-bromo-4-hydroxymethyl-2,3-dimethylbenzofuran are added at 0° within

15 minutes to a solution of 0.8 ml of phosphorus tribromide in 20 ml of absolute ether. After stirring for 2 hours at 0° and for a further 30 minutes at room temperature, the mixture is partitioned between ethyl acetate and ice-cooled water. The organic phase is washed in succession with water, aqueous sodium hydrogen carbonate solution and twice with brine. After drying over sodium sulfate and evaporation of the solvent under reduced pressure, the pure title compound is obtained. TLC (silica gel, chloroform/methanol 95:5) $R_f = 0.85$. IR (CH_2Cl_2): 1630, 1601, 1487, 1444, 1402, 1203 cm^{-1}.

Example 2: 7-Cyano-4-[1-(1,2,4-triazolyl)methyl]-2,3-dimethylbenzofuran

A mixture of 306.2 mg of 7-bromo-4-[1-(1,2,4-triazolyl)methyl]-2,3-dimethylbenzofuran (see Example 1) and 121.8 mg of copper(I) cyanide in 0.8 ml of pyridine is refluxed under nitrogen for 18 hours. The black reaction mixture is treated with ethyl acetate and 37 % aqueous ammonia solution and the organic phase is separated off. The organic phase is washed again with aqueous ammonia solution, then twice with 0.1N hydrochloric acid and finally twice with water, and is dried and filtered. After evaporation of the solvent under reduced pressure, the title compound is obtained. TLC (CH_2Cl_2/methanol 95:5) $R_f = 0.38$. IR (CH_2Cl_2): 2233, 1615, 1504, 1408 cm^{-1}.

Example 3: 7-Bromo-4-(1-imidazolylmethyl)-2,3-dimethylbenzofuran

1.76 g of sodium are added in portions to a solution of 22.3 g of imidazole in 350 ml of absolute THF which is being maintained at 45°. After stirring at 45° for 2.5 hours, the orange-coloured reaction mixture is treated with a solution of 16.7 g of 7-bromo-4-bromomethyl-2,3-dimethylbenzofuran (see Example 1d) in 250 ml of absolute THF. After 2 hours, the solvent is evaporated under reduced pressure and the reaction mixture is treated with aqueous sodium chloride solution and 180 ml of 1N sodium hydrogen carbonate solution. The reaction mixture is extracted three times with ether and the extracts are washed with brine, dried over sodium sulfate and concentrated to dryness by evaporation to yield the title compound, m.p. 158-160°. TLC (chloroform/methanol 9:1) $R_f = 0.49$. IR (CH_2Cl_2): 1630, 1500, 1400, 1385, 1230, 1209, 1150 cm^{-1}.

Example 4: 4-(1-Imidazolylmethyl)-7-phenoxy-2,3-dimethylbenzofuran hydrochloride

A mixture of 25.4 g of 7-bromo-4-(1-imidazolylmethyl)-2,3-dimethylbenzofuran (see Example 3), 11 g of potassium phenolate and 250 mg of copper powder is stirred for 18 hours at 150°. The reaction mixture is cooled to room temperature and chromatographed over silica gel (CH_2Cl_2/methanol 99.5:0.5), to yield the title compound in the form of the free base. The latter, dissolved in methanol, is treated with ethereal HCl

solution to yield the title compound; m.p. 180-181° (after crystallisation from methanol/ether); IR (Nujol): 2550, 1470, 1380, 1220 cm^{-1}.

Example 5: 7-Cyano-4-(1-imidazolylmethyl)-2,3-dimethylbenzofuran hydrochloride
A mixture of 1 g of 7-bromo-4-(1-imidazolylmethyl)-2,3-dimethylbenzofuran (see Example 3) and 0.32 g of copper(I)cyanide in 3 ml of N-methyl-2-pyrrolidone is stirred for 20 hours at 200°. The reaction mixture is cooled, poured into an ice-cooled 50 % aqueous ethylenediamine solution and extracted with methylene chloride. The organic extracts are washed twice with 50 % aqueous ethylenediamine solution and twice with water, dried over sodium sulfate and concentrated to dryness by evaporation to yield the title compound in crude form. The latter is chromatographed over silica gel (chloroform/methanol 95:5) to yield the title compound in pure form. TLC (chloroform/methanol 95:5) $R_f = 0.31$. IR (CH_2Cl_2): 2250, 1625, 1505, 1235, 1210 cm^{-1}. The hydrochloride of the title compound is obtained in a manner analogous to that described in Example 4; m.p. 258-260° (with decomposition).

Example 6: 7-Bromo-3-(1-imidazolylmethyl)-benzofuran hydrochloride
0.63 g of sodium is added within 30 minutes at 20° to a solution of 4.35 g of imidazole in 45 ml of absolute THF. After stirring for 2.5 hours - once all the sodium has been consumed - there is added dropwise to the reaction mixture, within 20 minutes, a solution of 7.9 g of 7-bromo-3-bromomethyl-benzofuran in 25 ml of THF. After stirring for a further 1.5 hours at room temperature, 300 ml of water are added to the reaction mixture, which is then extracted twice with 300 ml of ethyl acetate each time. The combined organic extracts are washed 5 times more with 50 ml of water each time and once with 70 ml of brine, are dried over sodium sulfate and concentrated. Purification is effected by column chromatography (silica gel, chloroform/methanol 9:1). The free base is dissolved in ethanol/ether and converted into the title compound by treatment with 6N ethereal HCl solution; m.p. 192-197° (with decomposition). IR (Nujol): 2960, 1465, 1415, 1370, 1285, 1280 cm^{-1}.

The starting compounds are prepared as follows:

(a) 2-(2-Bromophenoxy)-acetic acid ethyl ester
245.2 g of chloroacetic acid ethyl ester and 552 g of potash are added to 346 g of o-bromophenol in 1 litre of acetone. The yellow suspension is heated to reflux temperature and stirred at that temperature for 24 hours. The suspension is filtered with suction and the

residue is then washed repeatedly with acetone. The solution is concentrated under a high vacuum and the resulting oil is dissolved in ether and washed in succession, while cooling with ice, with 3 x 150 ml of 2N NaOH and 3 x 150 ml of brine. The ethereal phase is dried over sodium sulfate, filtered and concentrated by evaporation. The pure title compound is obtained by distillation under reduced pressure; b.p. 0.107 mbar 93-97°. TLC (silica gel/chloroform): $R_f = 0.69$.

(b) 3-(2-Bromophenoxy)-2-oxo-succinic acid diethyl ester

99 ml of ethanol are added dropwise within 20 minutes to a suspension of 86.6 g of 50 % sodium hydride in 2 litres of ether. During that procedure, the temperature rises to 25°. To the resulting suspension there are added dropwise within 25 minutes 245 ml of oxalic acid diethyl ester. The reaction mixture is heated to reflux temperature and then a solution of 425.3 g of 2-(2-bromophenoxy)-acetic acid ethyl ester in 500 ml of ether is added thereto. After 30 minutes - when everything has dissolved - the reaction mixture is cooled and is poured, with stirring, onto 1.5 kg of ice. A pH of 3 is established by the addition of 2N HCl and the phases are subsequently separated. The organic phase is washed with water and then with brine and is dried with sodium sulfate. After concentration under reduced pressure, the resulting title compound [IR (CH_2Cl_2): 1750, 1670, 1590 cm^{-1}] is further reacted without additional purification.

(c) 7-Bromo-2,3-di(ethoxycarbonyl)benzofuran

366.4 g of 3-(2-bromophenoxy)-2-oxo-succinic acid diethyl ester are added dropwise within 1 hour with stirring and at room temperature to 1.135 litres of 90 % sulfuric acid. The dark-brown reaction mixture is then stirred at 55° for 1 day. After cooling, the reaction mixture is poured, with stirring, onto 2 kg of ice. After extraction with ether and separation of the aqueous layer, the batch is washed in succession with brine, 1N aqueous sodium hydrogen carbonate solution and brine until neutral. After drying over sodium sulfate, filtration and concentration under reduced pressure, the crude product so obtained is purified by chromatography (silica gel/chloroform). TLC (chloroform) $R_f = 0.67$.
IR (CH_2Cl_2): 1740, 1600, 1475, 1370 cm^{-1}.

(d) 7-Bromo-3-ethoxycarbonyl-benzofuran

A mixture of 87.7 g of 7-bromo-2,3-di(ethoxycarbonyl)benzofuran, 30 g of sodium chloride and 9.2 ml of water is stirred in 530 ml of DMSO for 3 hours at 150° (CO_2 evolution). After cooling the reaction mixture, the undissolved material is removed by filtration over Hyflo Super Cel® (kieselguhr). The filtrate is freed of DMSO at 40° under

reduced pressure. The residue is dissolved in ethyl acetate and washed with 3 x 300 ml of water and 1 x 300 ml of brine. The organic phase is dried over sodium sulfate and concentrated under reduced pressure. The black residue is purified by column chromatography (silica gel/chloroform). The title compound is recrystallised from petroleum ether; m.p. 54-56°. IR (CH_2Cl_2): 1725, 1590, 1585, 1480 cm^{-1}.

(e) 7-Bromo-3-hydroxymethyl-benzofuran

28 g of 7-bromo-3-ethoxycarbonyl-benzofuran are added within 60 minutes at 0° under nitrogen to 182.6 ml of a 20 % solution of diisobutylaluminium hydride in toluene. After stirring for a further 60 minutes at 0°, the reaction mixture is poured onto a mixture of 400 ml of ice and 50 ml of 70 % sulfuric acid. After stirring and separation of the organic phase, extraction is carried out three times more with 50 ml of toluene each time. The combined extracts are washed with 4 x 35 ml of water and 1 x 30 ml of brine, dried over sodium sulfate and concentrated under reduced pressure. The residue is crystallised from ethyl acetate/petroleum ether; m.p. 111- 112°. IR (CH_2Cl_2): 3600, 1615, 1595, 1470 cm^{-1}.

(f) 7-Bromo-3-bromomethyl-benzofuran

6.25 g of 7-bromo-3-hydroxymethyl-benzofuran are added within 30 minutes at 3° to a solution of 2.73 g of phosphorus tribromide in 50 ml of ether. After the temperature has risen to 15°, the reaction mixture is stirred for a further 1 hour at 5° and is then poured onto 100 ml of ice. After the addition of ether, the phases are separated. The organic solution is washed with 3 x 40 ml of water and 1 x 40 ml of brine, is dried over sodium sulfate and concentrated. The title compound is crystallised from ethyl acetate/petroleum ether; m.p. 123-124.5°; IR (CH_2Cl_2): 1590, 1480, 1415 cm^{-1}.

Example 7: 7-Cyano-3-(1-imidazolylmethyl)-benzofuran hydrochloride

Analogously to Example 5, 5.98 g of 7-bromo-3-(1-imidazolylmethyl)-benzofuran (see Example 6) are converted with 2.13 g of copper(I) cyanide in 19.5 ml of N-methyl-2-pyrrolidone into the title compound which is crystallised from ethanol/ether; m.p. 237-239°; IR (KBr): 3090, 3000, 2800, 2236, 1575, 1425, 1280 cm^{-1}.

Example 8: 7-Bromo-5-(1-imidazolylmethyl)-2,3-dimethyl-benzofuran hydrochloride

Analogously to Example 6, 31.8 g of 7-bromo-5-bromomethyl-2,3-dimethyl-benzofuran are converted into the title compound; m.p. (after crystallisation from methanol/ether) 272-274°. IR (Nujol): 2962, 1464, 1416, 1370, 1287, 1281 cm^{-1}.

The starting compound is prepared as follows:

(a) 7-Bromo-5-bromomethyl-2,3-dimethyl-benzofuran
Analogously to Example 1d, 76.5 g of 7-bromo-5-hydroxymethyl-2,3-dimethylbenzofuran are converted into the title compound; m.p. 122-124°. IR (CH_2Cl_2): 1629, 1600, 1488, 1443, 1404, 1203 cm^{-1}.

Example 9: 7-Cyano-5-(1-imidazolylmethyl)-2,3-dimethyl-benzofuran hydrochloride
Analogously to Example 5, 12.2 g of 7-bromo-5-(1-imidazolylmethyl)-2,3-dimethyl-benzofuran (see Example 8) are converted with 3.9 g of copper(I) cyanide into the title compound; m.p. (after crystallisation from ethanol/ether) 258-259°. IR (KBr): 3092, 2238, 1470, 1285 cm^{-1}.

Example 10: 5-Bromo-3-(1-imidazolylmethyl)-benzofuran hydrochloride
Analogously to Example 6, 33.05 g of 5-bromo-3-bromomethyl-benzofuran are converted into the title compound; m.p. (after crystallisation from ethanol/ether) 190.5-191.5°; IR (KBr): 2750, 1450, 1270, 1110 cm^{-1}.

The starting compounds are prepared as follows:

(a) 2-(4-Bromophenoxy)-acetic acid ethyl ester
Analogously to Example 6a, 364.04 g of 4-bromophenol are converted into the title compound; m.p. (after crystallisation from hexane) 56-58°; IR (CH_2Cl_2): 1760, 1580, 1490, 1210 cm^{-1}.

(b) 3-(4-Bromophenoxy)-2-oxo-succinic acid diethyl ester
Analogously to Example 6b, 356.2 g of 2-(4-bromophenoxy)-acetic acid ethyl ester are converted into the title compound; IR (CH_2Cl_2): 1745, 1665, 1585, 1475, 1230 cm^{-1}.

(c) 5-Bromo-2,3-di(ethoxycarbonyl)benzofuran
Analogously to Example 6c, 465 g of 3-(4-bromophenoxy)-2-oxo-succinic acid diethyl ester are converted into the title compound; m.p. (after crystallisation from ether/petroleum ether) 45-48°; IR (CH_2Cl_2): 1725, 1580, 1300 cm^{-1}.

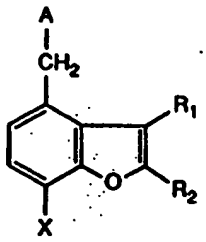
(d) 5-Bromo-3-ethoxycarbonyl-benzofuran
Analogously to Example 6d, 87.2 g of 5-bromo-2,3-di(ethoxycarbonyl)benzofuran are converted into the title compound; m.p. (after crystallisation from petroleum ether) 81-83°; IR (CH_2Cl_2): 1725, 1560, 1440 cm^{-1}.

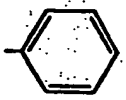
(e) 5-Bromo-3-hydroxymethyl-benzofuran
Analogously to Example 6e, 84.5 g of 5-bromo-3-ethoxycarbonyl-benzofuran are converted into the title compound; m.p. (after crystallisation from ethyl acetate/petroleum ether) 72-75°; IR (CH_2Cl_2): 3555, 1440, 1190 cm^{-1}.

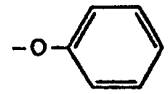
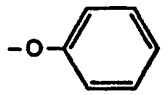
(f) 5-Bromo-3-bromomethyl-benzofuran
Analogously to Example 6f, 52.3 g of 5-bromo-3-hydroxymethyl-benzofuran are converted into the title compound; m.p. (after crystallisation from hexane) 75-78°; IR (CH_2Cl_2): 1445, 1180, 1105 cm^{-1}.

Example 11: 5-Cyano-3-(1-imidazolylmethyl)-benzofuran hydrochloride
Analogously to Example 5, 19.2 g of 5-bromo-3-(1-imidazolylmethyl)-benzofuran (see Example 10) are converted with 6.8 g of copper(I) cyanide in 60.6 ml of N-methyl-2-pyrrolidone into the title compound; m.p. (after crystallisation from ethanol/ether) 222-224°; IR: 2240, 1500, 1470 cm^{-1}.

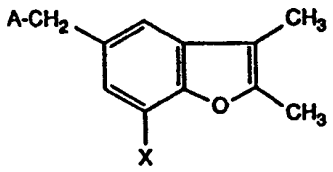
Example 12: The following compounds can be prepared in a manner analogous to that described in the Examples:



	A	X	R_1	R_2	IR (CH_2Cl_2) [cm^{-1}]
(a)	1-Imidazolyl	Cl	CH_3	CH_3	1629, 1502, 1231
(b)	1-Imidazolyl	Br	H	H	1630, 1501, 1232
(c)	1-Imidazolyl	Br	H	CH_3	1628, 1501, 1231
(d)	1-Imidazolyl	Br	CH_3	H	1630, 1500, 1231
(e)	1-Imidazolyl	Br	$-(CH_2)_4-$		1630, 1503, 1230
(f)	1-Imidazolyl	Br	C_2H_5	C_2H_5	1630, 1501, 1228
(g)	1-Imidazolyl	CN	H	CH_3	2248, 1625, 1504, 1234
(h)	1-Imidazolyl	CN	CH_3	H	2249, 1627, 1501, 1233
(i)	1-Imidazolyl	CN	H	H	2247, 1628, 1500, 1235
(j)	1-Imidazolyl	CN	$-(CH_2)_4-$		2250, 1629, 1502, 1231
(k)	1-(1,2,4-Triazolyl)	Cl	CH_3	CH_3	1631, 1605, 1504, 1199
(l)	1-(1,2,4-Triazolyl)	Br	H	CH_3	1628, 1607, 1502, 1200
(m)	1-(1,2,4-Triazolyl)	Br	CH_3	H	1629, 1605, 1502, 1200
(n)	1-(1,2,4-Triazolyl)	Br	$-(CH_2)_4-$		1630, 1604, 1504, 1198
(o)	1-(1,2,4-Triazolyl)	Br	H	H	1631, 1605, 1503, 1199
(p)	1-(1,2,4-Triazolyl)	CN	H	H	2233, 1615, 1504
(q)	1-(1,2,4-Triazolyl)	CN	H	CH_3	2235, 1617, 1503
(r)	1-(1,2,4-Triazolyl)	CN	CH_3	H	2232, 1615, 1503
(s)	1-(1,2,4-Triazolyl)	CN	$-(CH_2)_4-$		2233, 1614, 1504
(t)	1-(1,2,4-Triazolyl)		CH_3	CH_3	1602, 1505, 1227
(u)	1-(1,2,3-Triazolyl)	Br	CH_3	CH_3	1631, 1605, 1504, 1199
(v)	1-(1,2,3-Triazolyl)	CN	H	CH_3	2236, 1618, 1504
(w)	1-(1,2,3-Triazolyl)	CN	CH_3	H	2235, 1616, 1506
(x)	1-(1,2,3-Triazolyl)	CN	CH_3	CH_3	2236, 1617, 1505
(y)	1-(1,2,3-Triazolyl)	CN	$-(CH_2)_4-$		2235, 1617, 1505
(z)	1-(1,2,3-Triazolyl)		CH_3	CH_3	1602, 1506, 1228
(aa)	1-Tetrazolyl	Br	CH_3	CH_3	1630, 1606, 1504, 1200
(ab)	1-Tetrazolyl	CN	H	CH_3	2234, 1616, 1505
(ac)	1-Tetrazolyl	CN	CH_3	H	2232, 1616, 1506
(ad)	1-Tetrazolyl	CN	CH_3	CH_3	2232, 1618, 1505

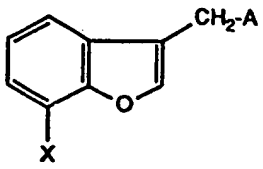
	A	X	R_1	R_2	IR (CH_2Cl_2) [cm^{-1}]
(ae)	1-Tetrazolyl	CN	$-(CH_2)_4-$		2235, 1617, 1503
(af)	1-Tetrazolyl		CH_3	CH_3	1602, 1505, 1225
(ag)	2-Tetrazolyl	Br	CH_3	CH_3	1628, 1606, 1504, 1201
(ah)	2-Tetrazolyl	CN	H	CH_3	2234, 1616, 1505
(ai)	2-Tetrazolyl	CN	CH_3	H	2232, 1614, 1505
(aj)	2-Tetrazolyl	CN	$-(CH_2)_4-$		2234, 1616, 1507
(ak)	2-Tetrazolyl		CH_3	CH_3	1602, 1507, 1227

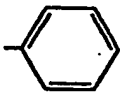
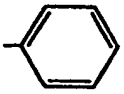
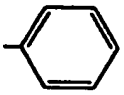
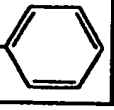
Example 13: The following compounds can be prepared in a manner analogous to that described in the preceding Examples:



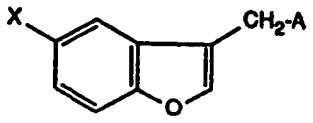
	A	X	IR [cm^{-1}]
(a)	1-(1,2,4-Triazolyl)	Br	1635, 1604, 1507
(b)	1-(1,2,4-Triazolyl)	CN	2238, 1617, 1505
(c)	1-Tetrazolyl	Br	1633, 1604, 1505
(d)	1-Tetrazolyl	CN	2237, 1619, 1504
(e)	2-Tetrazolyl	Br	1634, 1606, 1505
(f)	2-Tetrazolyl	CN	2236, 1618, 1504

Example 14: The following compounds can be prepared in a manner analogous to that described in the preceding Examples:



	A	X	IR [cm^{-1}]
(a)	1-Imidazolyl		1602, 1506, 1495, 1227
(b)	1-(1,2,4-Triazolyl)	Br	1632, 1605, 1504, 1198
(c)	1-(1,2,4-Triazolyl)	CN	2236, 1618, 1505
(d)	1-(1,2,4-Triazolyl)		1601, 1507, 1496, 1228
(e)	1-Tetrazolyl	Br	1630, 1606, 1505, 1197
(f)	1-Tetrazolyl	CN	2235, 1615, 1505
(g)	1-Tetrazolyl		1600, 1507, 1494, 1227
(h)	2-Tetrazolyl	Br	1631, 1606, 1504, 1199
(i)	2-Tetrazolyl	CN	2235, 1617, 1508
(j)	2-Tetrazolyl		1602, 1506, 1495, 1228

Example 15: The following compounds can be prepared in a manner analogous to that described in the preceding Examples:



	A	X	IR [cm^{-1}]
(a)	1-(1,2,4-Triazolyl)	Br	1632, 1606, 1503, 1198
(b)	1-(1,2,4-Triazolyl)	CN	2237, 1614, 1502
(c)	1-(1,2,3-Triazolyl)	Br	1630, 1605, 1502, 1200
(d)	1-(1,2,3-Triazolyl)	CN	2234, 1615, 1504
(e)	1-Tetrazolyl	Br	1631, 1606, 1502, 1197
(f)	1-Tetrazolyl	CN	2235, 1615, 1503
(g)	2-Tetrazolyl	Br	1632, 1605, 1504, 1202
(h)	2-Tetrazolyl	CN	2237, 1614, 1504

Example 16: (a) 7-Bromo-4-(2-tetrazolylmethyl)-2,3-dimethylbenzofuran and (b) 7-bromo-4-(1-tetrazolylmethyl)-2,3-dimethylbenzofuran

315 mg of dry tetrazole, 417 mg of potassium carbonate and 30 mg of potassium iodide are added in succession to a solution of 955 mg of 7-bromo-4-bromomethyl-2,3-dimethylbenzofuran in 15 ml of acetone. After stirring at 55° for 1.17 hours, the reaction mixture is cooled and concentrated. The residue is taken up in CH_2Cl_2/water. The organic phase is separated off, washed with brine, dried over sodium sulfate and concentrated. Column chromatography (SiO_2, CH_2Cl_2) yields first 7-bromo-4-(2-tetrazolylmethyl)-2,3-dimethylbenzofuran; m.p. (after recrystallisation from ether/hexane): 117-120°; ^{1}H-NMR (DMSO-d_6): w = 2.25 (s, 3H), 2.42 (s, 3H), 6.27 (s, 2H), 7.07 and 7.47 (arom. H, 2H), 9.0 (s, 1H) ppm; and then 7-bromo-4-(1-tetrazolylmethyl)-2,3-dimethylbenzofuran; m.p. (after recrystallisation from ether): 168-170°; ^{1}H-NMR (DMSO- d_6): w = 2.25 (s, 3H), 2.44 (s, 3H), 6.03 (s, 2H), 6.97 and 7.47 (arom. H, 2H), 9.47 (s, 1H) ppm.

Example 17: 7-Cyano-4-(2-tetrazolylmethyl)-2,3-dimethylbenzofuran

A solution of 154 mg of 7-bromo-4-(2-tetrazolylmethyl)-2,3-dimethylbenzofuran and 50 mg of copper(I) cyanide in 0.9 ml of N-methyl-2-pyrrolidone is stirred at 190-200° for 2.5 hours. After cooling, the reaction mixture is diluted with CH_2Cl_2, washed twice with aqueous ethylenediamine solution (50 %), twice with water and twice with brine and, after being dried over sodium sulfate, is concentrated. The title compound is purified by column chromatography (SiO_2, toluene to toluene/ethyl acetate 95:5) and subsequently crystallised from CH_2Cl_2/ether/hexane; m.p. 134-135°; TLC (silica gel, methylene chloride): R_f = 0.3. IR (CH_2Cl_2): 2234, 1631, 1616, 1407 cm^{-1}.

Example 18: 7-Carbamoyl-4-(1-imidazolylmethyl)-2,3-dimethylbenzofuran hydrochloride

18 mg of potassium carbonate and 48 ml of a 30 % aqueous H_2O_2 solution are added at

room temperature to a suspension of 95 mg of 7-cyano-4-(1-imidazolylmethyl)-2,3-dimethylbenzofuran hydrochloride in 0.5 ml of DMSO and 1 ml of CH_2Cl_2. After the further addition of 20 mg of potassium carbonate and 0.2 ml of H_2O_2 solution, the bath temperature is adjusted to 50-60° and, after the further addition of 0.2 ml of H_2O_2 solution, the reaction mixture is stirred at room temperature for 19 hours to complete the reaction. 3 ml of water are added to the reaction mixture which is then stirred for 1 hour while cooling with ice. The solid is removed by filtration, washed with water and dried over P_2O_5 in a hot desiccator. The solid is crystallised from methylene chloride/methanol/ether. After dissolving in methylene chloride/methanol, there are added to the solid 40 ml of 9N methanolic HCl solution; after the addition of ether, the title compound crystallises out. After filtering off, washing with ether and drying in a desiccator, the title compound is obtained. TLC (silica gel, methylene chloride/methanol 9:1) $R_f = 0.31$; IR (KBr): 3420, 1660, 1610, 1575, 1410 cm^{-1}.

Example 19: 7-Carbamoyl-4-[1-(1,2,4-triazolyl)methyl]-2,3-dimethylbenzofuran

20 mg of potassium carbonate and 48 ml of a 30 % hydrogen peroxide solution are added to a solution of 100.5 mg of 7-cyano-4-[1-(1,2,4-triazolyl)methyl]-2,3-dimethylbenzofuran (Example 2) in 0.5 ml of DMSO and a small amount of CH_2Cl_2. After stirring at room temperature for 17.5 hours, a further 48 ml of a 30 % hydrogen peroxide solution are added and the reaction mixture is stirred again for 3 hours. While cooling with ice, 3 ml of water are then added to the beige suspension, which is then stirred for 45 minutes and filtered. After being washed, the filtration residue is dried over phosphorus pentoxide. After stirring with CH_2Cl_2, the pure title compound is obtained; IR (KBr): 3427, 3188, 1694, 1616, 1503, 1407, 1272 cm^{-1}.

Example 20: 7-N-(cyclohexylmethyl)carbamoyl-4-[1-(1,2,4-triazolyl)methyl]-2,3-dimethylbenzofuran

69 ml of aminomethylcyclohexane, 114 mg of N,N'-dicyclohexylcarbodiimide, 3 mg of 4-N,N-dimethylaminopyridine and 8 mg of N-hydroxybenzotriazole are added to an ice-cooled suspension of 136 mg of 7-carboxy-4-[1-(1,2,4-triazolyl)methyl]-2,3-dimethyl-benzofuran in 4 ml of CH_2Cl_2 and 1 ml of DMF. After 10 minutes, the cooling bath is removed and the reaction mixture is stirred at room temperature for 7 hours. A further 57 mg of N,N'-dicyclohexylcarbodiimide, 35 ml of aminomethylcyclohexane and 2 mg of 4-N,N-dimethylaminopyridine are then added to the reaction mixture. After 6 hours, the solid is removed by filtration. The filtrate is diluted with CH_2Cl_2 and washed in succession with aqueous sodium hydrogen carbonate solution, water and brine. After

drying and concentration, the crude product is purified by column chromatography (SiO_2, CH_2Cl_2 to CH_2Cl_2/methanol 95:5) and subsequent digestion in hexane; IR (CH_2Cl_2): 3439, 2925, 1661, 1610, 1540, 1504, 1449 cm^{-1}.

The starting compound is prepared as follows:

(a) 7-Carboxy-4-[1-(1,2,4-triazolyl)methyl]-2,3-dimethylbenzofuran
A solution of 252 mg of 7-cyano-4-[1-(1,2,4-triazolyl)methyl]-2,3-dimethylbenzofuran (Example 2) in 4 ml of ethanol and 4 ml of 4N NaOH is stirred under reflux conditions for 20.25 hours. After cooling by means of cooling with ice-water, a pH of 3 is established with 2N H_2SO_4. The ethanol is evaporated off and the resulting white suspension is cooled in a refrigerator for 1.5 hours. The crude product is obtained by filtration and is purified by being stirred in CH_2Cl_2; IR (KBr): 3429, 3140, 1693, 1610, 1512, 1405, 1292 cm^{-1}.

Example 21: 7-N-(cyclohexylmethyl)carbamoyl-4-(1-imidazolylmethyl)-2,3-dimethylbenzofuran
109 mg of potassium hydroxide are added to a solution of 100 mg of 7-cyano-4-(1-imidazolylmethyl)-2,3-dimethylbenzofuran (Example 5) in 0.3 ml of tert-butanol and the mixture is stirred at 80° for 20 minutes. After cooling, 0.3 ml of bromomethylcyclohexane are added dropwise to the mixture which is then stirred under reflux for 30 minutes. After cooling, the mixture is poured onto water and extracted with CH_2Cl_2. The organic phase is dried and concentrated. The crude product is purified by column chromatography (SiO_2, CH_2Cl_2 to CH_2Cl_2/methanol 95:5); IR (CH_2Cl_2): 3439, 2924, 1661, 1610, 1541, 1505, 1449, 1389 cm^{-1}.

Example 22: 7-N-(n-propyl)carbamoyl-4-(1-imidazolylmethyl)-2,3-dimethylbenzofuran
Analogously to Example 21, 100 mg of 7-cyano-4-(1-imidazolylmethyl)-2,3-dimethylbenzofuran in 0.3 ml of tert-butanol are converted with 109 mg of potassium hydroxide and 178 ml of n-propyl bromide into the title compound. The latter is purified by column chromatography (SiO_2, CH_2Cl_2 to CH_2Cl_2/methanol 98:2) and stirring in hexane; IR (CH_2Cl_2): 3435, 3040, 1660, 1610, 1539, 1505, 1457, 1389 cm^{-1}.

Example 23: 7-N-(2-propyl)carbamoyl-4-(1-imidazolylmethyl)-2,3-dimethylbenzofuran
Analogously to Example 21, 135 mg of 7-cyano-4-(1-imidazolylmethyl)-2,3-dimethylbenzofuran in 0.4 ml of tert-butanol are converted with 148 mg of potassium hydroxide

and a total of 515 ml of isopropyl iodide within 8 hours into the title compound. The latter is purified by column chromatography (SiO_2, CH_2Cl_2 to CH_2Cl_2/methanol 98:2); IR (CH_2Cl_2): 4325, 2966, 1658, 1610, 1535, 1505, 1457, 1387 cm^{-1}.

Example 24: 10 000 tablets are prepared, each containing 5 mg of active ingredient, for example one of the compounds prepared in Examples 1-23:

Composition:

active ingredient	50.00	g
lactose	2535.00	g
corn starch	125.00	g
polyethylene glycol 6000	150.00	g
magnesium stearate	40.00	g
purified water	quantum satis	

Procedure: All the pulverulent constituents are sieved through a sieve of 0.6 mm mesh width. Then the active ingredient, the lactose, the magnesium stearate and half of the starch are mixed in a suitable mixer. The other half of the starch is suspended in 65 ml of water and the resulting suspension is added to a boiling solution of the polyethylene glycol in 260 ml of water. The paste formed is added to the powder mixture and the resulting mixture is granulated, if desired or necessary with the addition of more water. The granulate is dried overnight at 35°C, forced through a sieve of 1.2 mm mesh width and pressed into tablets having a breaking notch.

Example 25: 1000 capsules are prepared, each containing 10 mg of active ingredient, for example one of the compounds prepared in Examples 1-23:

Composition:

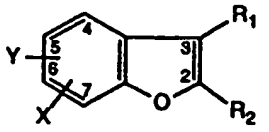
active ingredient	10.00	g
lactose	207.00	g
modified starch	80.00	g
magnesium stearate	3.00	g

Procedure: All the pulverulent constituents are sieved through a sieve of 0.6 mm mesh width. Then, in a suitable mixer, the active ingredient is mixed first with the magnesium stearate and then with the lactose and the starch until homogeneous. No. 2 hard gelatin

capsules are each filled with 300 mg of the resulting mixture using a capsule-filling machine.

What is claimed is:

1. A compound of formula I



(I)

wherein X is halogen, cyano, carbamoyl, N-lower alkylcarbamoyl, N,N-di-lower alkylcarbamoyl, N,N-lower alkylenecarbamoyl; N,N-lower alkylenecarbamoyl interrupted by -O-, -S- or -NR"- wherein R" is hydrogen, lower alkyl or lower alkanoyl; N-cycloalkylcarbamoyl, N-(lower alkyl-substituted cycloalkyl)-carbamoyl, N-cycloalkyl-lower alkylcarbamoyl, N-(lower alkyl-substituted cycloalkyl)-lower alkylcarbamoyl, N-aryl-lower alkylcarbamoyl, N-arylcarbamoyl, N-hydroxycarbamoyl, hydroxy, lower alkoxy, aryl-lower alkoxy or aryloxy, Y is a $-CH_2$-A group in which A is imidazolyl, triazolyl or tetrazolyl bonded by way of a ring nitrogen atom, or Y is hydrogen, each of R_1 and R_2 independently of the other is hydrogen, lower alkyl or a $-CH_2$-A group as defined for Y, or R_1 and R_2 together are lower alkylene, with the proviso that one of the radicals Y, R_1 and R_2 is a $-CH_2$-A group, with the further proviso that, in a $-CH_2$-A group as the meaning of R_1 or R_2, A is other than 1-imidazolyl when X is bromine, cyano or carbamoyl, and with the proviso that, in a $-CH_2$-A group as the meaning of Y, A is other than 1-imidazolyl when X is halogen or lower alkoxy, R_1 is hydrogen and R_2 is hydrogen or lower alkyl, or a salt thereof.

2. A compound of formula I according to claim 1, wherein X is halogen, cyano, carbamoyl, N-lower alkylcarbamoyl, N- cycloalkyl-lower alkylcarbamoyl, N,N-di-lower alkylcarbamoyl, N-arylcarbamoyl, hydroxy, lower alkoxy, aryl-lower alkoxy or aryloxy, wherein aryl is phenyl or naphthyl each of which is unsubstituted or substituted by lower alkyl, hydroxy, lower alkoxy, halogen and/or by trifluoromethyl; Y is a $-CH_2$-A group in which A is 1-imidazolyl, 1-(1,2,4-triazolyl), 1-(1,3,4-triazolyl), 1-(1,2,3-triazolyl), 1-(1,2,5-triazolyl), 1-tetrazolyl or 2-tetrazolyl, or Y is hydrogen; each of R_1 and R_2 independently of the other is hydrogen, lower alkyl or a $-CH_2$-A group as defined for Y, or R_1 and R_2 together are $-(CH_2)_n$- wherein n is 3, 4 or 5; with the proviso that one of the radicals Y, R_1 and R_2 is a $-CH_2$-A group, with the further proviso that, in a $-CH_2$-A group as the meaning of R_1 or R_2, A is other than 1-imidazolyl when X is bromine, cyano or

carbamoyl, and with the proviso that, in a -CH_2-A group as the meaning of Y, A is other than 1-imidazolyl when X is halogen or lower alkoxy, R_1 is hydrogen and R_2 is hydrogen or lower alkyl, or a salt thereof.

3. A compound of formula I according to claim 1, wherein the radical X is attached in the 5- or 7-position and is halogen, cyano, carbamoyl or phenyloxy; the radical Y is attached in the 4- or 5-position and is a -CH_2-A group in which A is 1-imidazolyl, 1-(1,2,4-triazolyl), 1-(1,2,3-triazolyl), 1-tetrazolyl or 2-tetrazolyl, or the radical Y is hydrogen; R_1 is hydrogen, lower alkyl or a -CH_2-A group as defined for Y, R_2 is hydrogen or lower alkyl, or R_1 and R_2 together are -$(CH_2)_4$-; with the proviso that one of the radicals Y and R_1 is a -CH_2-A group; with the further proviso that, in a -CH_2-A group as the meaning of R_1, A is other than 1-imidazolyl when X is bromine, cyano or carbamoyl, and with the proviso that, in a -CH_2-A group as the meaning of Y, A is other than 1-imidazolyl when X is halogen and R_1 is hydrogen; or a salt thereof.

4. A compound of formula I according to claim 1, wherein the radical X is attached in the 5- or 7-position and is halogen, cyano, carbamoyl or phenyloxy; the radical Y is attached in the 4- or 5-position and is a -CH_2-A group in which A is 1-(1,2,4-triazolyl), 1-(1,2,3-triazolyl), 1-tetrazolyl or 2-tetrazolyl, or the radical Y is hydrogen; R_1 is hydrogen, lower alkyl or a -CH_2-A group as defined for Y, R_2 is hydrogen or lower alkyl, or R_1 and R_2 together are -$(CH_2)_4$-; with the proviso that one of the radicals Y and R_1 is a -CH_2- A group; or a salt thereof.

5. A compound of formula I according to claim 1, wherein the radical X is attached in the 5- or 7-position and is halogen, cyano, carbamoyl or phenyloxy; the radical Y is attached in the 4- or 5-position and is a -CH_2-A group in which A is 1-imidazolyl, 1-(1,2,4-triazolyl), 1-(1,2,3-triazolyl), 1-tetrazolyl or 2-tetrazolyl; each of R_1 and R_2 independently of the other is hydrogen or lower alkyl, or R_1 and R_2 together are -$(CH_2)_4$-; with the proviso that, in a group Y = -CH_2-A, A is other than 1-imidazolyl when X is halogen and R_1 is hydrogen; or a salt thereof.

6. A compound of formula I according to claim 1, wherein the radical X is attached in the 5- or 7-position and is halogen, cyano, carbamoyl or phenyloxy; the radical Y is hydrogen; R_1 is a -CH_2-A group in which A is 1-imidazolyl, 1-(1,2,4-triazolyl), 1-(1,2,3-triazolyl), 1-tetrazolyl or 2- tetrazolyl, R_2 is hydrogen or lower alkyl; with the proviso that, in a group R_1 = -CH_2-A, A is other than 1-imidazolyl when X is bromine, cyano or

carbamoyl; or a salt thereof.

7. A compound of formula I according to claim 1, wherein the radical X is attached in the 7-position and is bromine, cyano, carbamoyl or phenyloxy; the radical Y is attached in the 4-position and is a $-CH_2$-A group in which A is 1-imidazolyl, 1-(1,2,4-triazolyl), 1-tetrazolyl or 2-tetrazolyl; each of R_1 and R_2 independently of the other is lower alkyl, or R_1 and R_2 together are $-(CH_2)_4-$; or a salt thereof.

8. A compound of formula I according to claim 1, wherein X is halogen, cyano, carbamoyl, hydroxy, lower alkoxy or phenyloxy, wherein phenyl is unsubstituted or substituted by lower alkyl, hydroxy, lower alkoxy, halogen and/or by trifluoromethyl, Y is a $-CH_2$-A group in which A is 1-imidazolyl, 1-(1,2,4-triazolyl), 1-(1,3,4-triazolyl), 1-(1,2,3-triazolyl), 1-(1,2,5-triazolyl), 1-tetrazolyl or 2-tetrazolyl, R_1 is lower alkyl, R_2 is hydrogen or lower alkyl, or R_1 and R_2 together are $-(CH_2)_n-$ wherein n is 3 or 4, or a salt thereof.

9. A compound of formula I according to claim 1, wherein the radical X is attached in the 4- or 7-position and is halogen, cyano, carbamoyl or phenyloxy; the radical Y is attached in the 4- or 5-position and is a $-CH_2$-A group in which A is 1-imidazolyl, 1-(1,2,4-triazolyl), 1-(1,2,3-triazolyl), 1-tetrazolyl or 2-tetrazolyl, R_1 is lower alkyl, R_2 is hydrogen or lower alkyl, or R_1 and R_2 together are $-(CH_2)_4-$; or a salt thereof.

10. 7-Cyano-4-[1-(1,2,4-triazolyl)methyl]-2,3-dimethylbenzofuran according to claim 1, or a pharmaceutically acceptable salt thereof.

11. 7-Cyano-4-(1-imidazolylmethyl)-2,3-dimethylbenzofuran according to claim 1, or a pharmaceutically acceptable salt thereof.

12. 7-Carbamoyl-4-(1-imidazolylmethyl)-2,3-dimethylbenzofuran according to claim 1, or a pharmaceutically acceptable salt thereof.

13. A pharmaceutical composition containing a compound according to any one of claims 1 to 12 and at least one pharmaceutically acceptable carrier.

14. A compound according to any one of claims 1 to 12 for use in a method for the therapeutic treatment of the animal or human body.

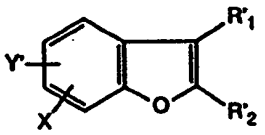
15. A compound according to any one of claims 1 to 12 for use in the treatment of diseases responsive to inhibition of the enzyme aromatase.

16. The use of a compound according to any one of claims 1 to 12 for the preparation of pharmaceutical compositions.

17. The use of a compound according to any one of claims 1 to 12 for the preparation of pharmaceutical compositions for the treatment of diseases responsive to inhibition of the enzyme aromatase.

18. A process for the preparation of a compound of formula I according to claim 1, which comprises

(a) condensing a reactive esterified derivative of a hydroxymethyl compound of formula II



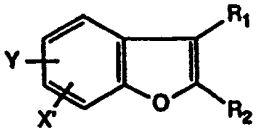
(II),

wherein one of the radicals Y', R'_1 and R'_2 is hydroxymethyl and the other two radicals have the definitions given for Y, R_1 and R_2, respectively, under formula I, and X is as defined under formula I, with a compound

A - H (III),

wherein A is as defined under formula I, or with an N-protected derivative thereof, or

(b) in a compound of formula IV

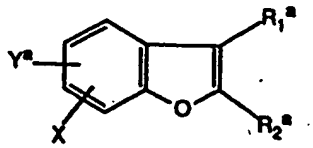


(IV),

wherein X' is a radical that can be converted into a group X, and Y, R_1 and R_2 are as

defined under formula I, converting the radical X' into a group X, or

(c) for the preparation of compounds of formula I wherein A in the group $-CH_2-A$ is 1-tetrazolyl, reacting a compound of formula V



(V),

wherein one of the radicals Y^a, $R_1{}^a$ and $R_2{}^a$ is isocyanomethyl and the other two radicals have the definitions given for Y, R_1 and R_2, respectively, under formula I, and X is as defined under formula I, with hydrazoic acid or, especially, with a salt thereof; and/or, if desired, converting a resulting compound of formula I into another compound of formula I, and/or, if desired, converting a resulting salt into the free compound or into another salt, and/or, if desired, converting a resulting free compound of formula I having salt-forming properties into a salt, and/or separating a resulting mixture of isomeric compounds of formula I into the individual isomers.

Fetherstonhaugh & Co.,
Ottawa, Canada
Patent Agents

L6 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1991:656181 CAPLUS
DOCUMENT NUMBER: 115:256181
TITLE: Preparation of (azolylmethyl)benzofurans as aromatase inhibitors
INVENTOR(S): Lang, Marc; Schilling, Walter
PATENT ASSIGNEE(S): Ciba-Geigy A.-G., Switz.
SOURCE: Eur. Pat. Appl., 21 pp.
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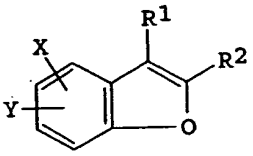
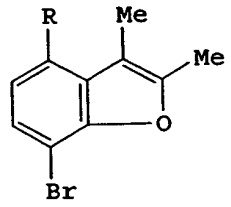
EP 445073	A1	19910904	EP 1991-810110	19910220
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
AU 9171246	A1	19910829	AU 1991-71246	19910220
CA 2036975	AA	19910828	CA 1991-2036975	19910225
JP 04211684	A2	19920803	JP 1991-33034	19910227
			CH 1990-627	19900227

PRIORITY APPLN. INFO.:
OTHER SOURCE(S): MARPAT 115:256181
GI



I

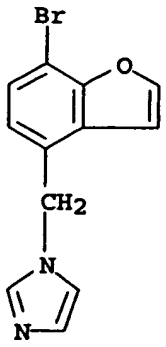


II

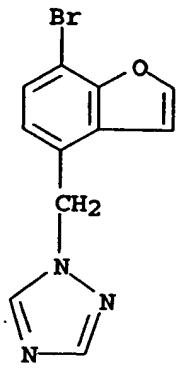
AB The title compds. [I; R1, R2 = H, alkyl, CH2A; A = imidazolyl, triazolyl, tetrazolyl; R1R2 = alkylene; X = OH, halo, cyano, alkoxy, (un)substituted CONH2; Y = H, CH2A] were prepd. Thus, 4,3-Br(HO)C6H3CO2Et was O-alkylated with MeCOCHMeCl and the product cyclized to give benzofuran II (R = CO2Et) which was converted in 2 steps to II (R = CH2Br). The latter was condensed with 1,2,4-triazole to give II (R = triazolomethyl). I gave regression of DMBA-induced mammary tumors in rats at daily doses from .apprx.1 mg/kg orally.

IT **137241-67-9P 137241-80-6P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of, as aromatase inhibitor)

RN 137241-67-9 CAPLUS
CN 1H-Imidazole, 1-[(7-bromo-4-benzofuranyl)methyl]- (9CI) (CA INDEX NAME)



RN 137241-80-6 CAPLUS
CN 1H-1,2,4-Triazole, 1-[(7-bromo-4-benzofuranyl)methyl]- (9CI) (CA INDEX NAME)



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